Analysis of the Compression Mechanics of Pharmaceutical Agglomerates of Different Porosity and Composition Using the Adams and Kawakita Equations

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Purpose. To analyze the mechanics of some pharmaceutical agglomerates during uniaxial confined compression by using compression parameters derived from the Heckel, Kawakita and Adams equations, and to study the influence of these compression parameters on the tablet-forming ability of agglomerates.

Methods. Force and displacement data sampled during in-die compression of agglomerates was used to calculate compression parameters according to the Heckel (σ_y), Kawakita ($1/b$ and a), and Adams (τ_0') equations. Mechanical strength of single agglomerates as well as the air permeability and tensile strength of tablets prepared from them were also determined.

Results. σ_y from the Heckel equation did not differ between agglomerates of different porosity. Both $1/b$ and τ_0' varied with agglomerate porosity and composition. These two compression parameters were linearly related to each other. No general correlation was found between $1/b$ and τ_0' and the strength of single agglomerates. The two parameters were related to the intergranular pore structure and tensile strength of tablets formed from the agglomerates.

Conclusions. $1/b$ and τ_0' may be interpreted as measures of the agglomerate shear strength during uniaxial confined compression, and as such they may be used as indicators of the tabletting performance of the agglomerates.

KEY WORDS: Heckel equation; Kawakita equation; Adams equation; agglomerate shear strength; tablet pore structure; tablet tensile strength.

INTRODUCTION

Agglomerates are handled in a variety of technical disciplines, such as pharmaceutical production. During handling and processing, agglomerates are subjected to stresses and it is often required that agglomerates can be handled or processed without fracturing, e.g., during transport, mixing or coating. Thus, the problems of forming agglomerates of sufficient strength, and assessing their strength, have been discussed in the literature (1,2). Normally, the strength of agglomerates is measured using single particles. However, alternative procedures by which the strength of an agglomerate can be derived from the analysis of compression data have been developed (3,4). Such procedures involve the compression of a bed of agglomerates in a confined space, and the strength of single agglomerates is estimated from the relationship between applied stress and strain in-die. It is thus reasonable that agglomerate strength is a property involved also in the tabletting of pharmaceutical agglomerates, such as granules and pellets, although its relevance in terms of the quality of the formed tablet is not satisfactorily understood.

We have described (5,6) the response to compression of agglomerates in-die as deformation rather than fragmentation. Deformation was thought to occur by a process where particles reposition or flow within the agglomerate, i.e., a process similar to fracturing by shearing (a mode II failure). However, it has also been reported that fracturing of agglomerates in-die can occur by a crack-opening mechanism, a mode I failure (7). It is possible that the stresses needed to initiate deformation or fracturing of agglomerates are similar in magnitude. Thus, the concept of an apparent strength of agglomerates during confined compression may apply to both fracturing and deformation.

The method of preference in order to assess the deformability of non-porous particles from confined compression data is the calculation of their mean yield strength from the tablet porosity-applied pressure relationship described by the Heckel equation (8). Some authors have, however, concluded that this equation is not suitable to describe the compression behavior of porous agglomerates (7,9). In the literature, a large number of other compression equations exist (10), although their interpretation in terms of single particle mechanical properties is not always clear. Exceptions in this context are the equations given by Lüdde and Kawakita (11) and Adams *et al.* (3) from which measures can be derived which can be interpreted in physical terms.

There is currently no recognised procedure in pharmaceutical science by which the confined compression strength of agglomerates such as granules or pellets can be derived and used in formulation engineering programs, such as expert systems. However, the two models discussed above (the Adams and Kawakita relationships) are promising approaches in this context. Thus, in this study, the strength of three types of agglomerates was derived from confined compression data by the approaches given by Adams and Kawakita, and compared with the Heckel yield strength of the agglomerates. The effects of porosity and composition of the agglomerates on their confined compression agglomerate strength was also studied. The physical interpretation of the term agglomerate strength was discussed and the relevance of the agglomerate strength in terms of the ability of the agglomerates to form tablets was investigated.

MATERIALS AND METHODS

Materials

In earlier papers from our laboratory, the properties of spherical agglomerates (also known as pellets), 0.71–1.00 mm diameter, prepared by extrusion-spherosisation of microcrystalline cellulose (MCC) (5) or of a 4 to 1 w/w mixture of dicalcium phosphate dihydrate and microcrystalline cellulose (DCP/MCC) (6) were presented and discussed. Some relevant characteristics of the agglomerates presented in those papers are summarized in Table 1. The porosities of MCC agglomerates of denominations 1–5 were varied by the use of mixtures of different amounts of water and ethanol as agglomeration liquids during preparation, where the use of increasing amounts of ethanol led to a higher agglomerate porosity. For agglomerate

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Table 1. Single Agglomerate and Bed Compression Data

Agglomerate type	Agglomerate denomination	Agglomerate porosity[c] (n = 3) (%)	τ_{0s}[d] (n = 100) (MPa)	Adams τ_0' values (n = 1–3) (MPa)	Kawakita 1/*b* values (n = 1–3) (MPa)	Linear part[e], Adams eq. (n = 1–3) (MPa)	Linear part,[e] Kawakita eq. (n = 1–3) (MPa)	Heckel σ_y values[f] (n = 1–3) (MPa)
MCC, set A[a]	1	11	25.5	36.4	36.5	21–89	19–200	73.5
	2	14	22.1	25.9	27.6	18–97	5–200	79.4
	3	27	10.5	9.79	14.7	23–98	13–200	68.5
	4	40	7.24	3.41	9.01	19–105	10–200	68.5
	5	46	3.86	1.62	6.66	23–105	8–200	67.1
MCC, set B[a]	I	12	24.7	43.0	41.5	29–102	6–200	76.3
	II	22	19.5	18.7	22.7	21–117	11–200	77.5
	III	33	18.9	11.4	15.8	18–77	9–200	73.0
	IV	46	13.3	5.57	9.59	17–83	6–200	76.3
DCP/MCC[b]	A	26	8.73	20.5	23.5	8–78	14–200	167
	B	36	5.42	10.1	17.9	8–109	30–200	161
	C	42	5.08	8.55	14.9	6–102	18–200	168
	D	48	7.82	6.08	11.0	10–54	10–200	159
	E	55	5.42	3.76	7.76	5–56	5–200	156

[a] Data from (5).
[b] Data from (6).
[c] From mercury pycnometry.
[d] Calculated from single agglomerate median fracture force (n = 100) according to Adams *et al.* (3).
[e] Pressure limits for linear region in profiles constructed from the compression equations ($R > 0.9998$).
[f] Due to a slight curvature throughout the Heckel profile, σ_y values were obtained from a set pressure range (50–150 MPa, $R > 0.997$).

denominations I-IV and A-E, porosity was varied by the incorporation of different amounts of a powder component (salicylic acid) before agglomeration that was later removed from the prepared agglomerates by extraction by ethanol.

Preparation of Tablets

500 mg agglomerates were compressed in an instrumented (with punch strain gauges and displacement transducers) single punch tablet press (Korsch EK 0, Germany), fitted with 11.3 mm circular flat faced punches. The agglomerates were manually filled into the prelubricated (by magnesium stearate) die and tabletted at machine speed. The position of the lower punch was adjusted to obtain the required maximum applied pressure; 100 MPa for tablets used for air permeability and tensile strength determinations, and 200 MPa for tablets used in the calculation of compression parameters.

After compaction, the 100 MPa tablets were stored in a desiccator at 40% relative humidity and room temperature for not less than 3 days before characterisation.

The Tensile Strength of Tablets

Tablets prepared at 100 MPa were compressed diametrically in a materials testing machine (model M30K, J. J. Lloyd Instruments Ltd, UK) at a loading rate of 5 mm/min. The tensile strength (n = 5–10) was derived from the force needed to fracture the tablets (12).

Air Permeability

The permeability of 100 MPa tablets to air flow (n = 3) was determined using a constant volume permeameter. The measurement procedure of Alderborn et el. (13) was used. The permeability coefficient (9) was then calculated for each compact.

Single Agglomerate Fracture Strength

Agglomerates from the thickness fraction 761–840 μm were compressed individually (diametral two-point loading) at 0.5 mm/min in a materials testing machine (M30K, J.J. Lloyd Instruments Ltd, UK) until a sharp decrease in loading force occurred. The peak compression force before the decrease was used as the fracture force of the aggregates.

The fracture force of aggregates was used to calculate the nominal fracture strength of single aggregates (τ_{0s}) (3):

$$\tau_{0s} = \frac{4F_f}{\pi d^2}$$

where F_f is the fracture force of an agglomerate and d is the mean diameter for the tested size fraction.

Calculation of Compression Parameters

The compression parameters derived from the Heckel, Kawakita and Adams equations (see below) were obtained through linear regression of force and displacement data adapted according to the linear forms of the equations (examples are given in Fig. 1). Relevant data are presented in Table 1.

In the evaluation of the Adams equation, the authors (3) used a limited pressure range well below the pressures required for the formation of tablets of acceptable strength. However, for agglomerates which are to be formed into tablets, the use of compression data at compaction pressures which correspond to the formation of tablets, i.e., considerably higher than the pressure region used by Adams *et al.*, seems logical to apply.

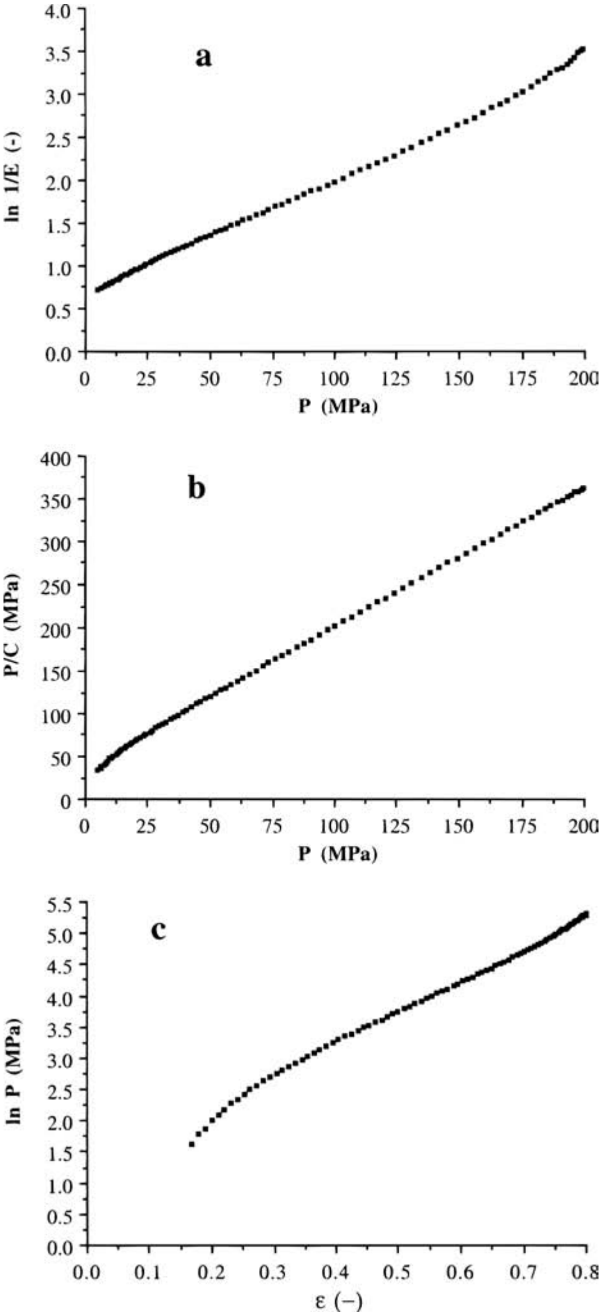

Fig. 1. Examples of linearized compression equations: (a) Heckel equation. (b) Kawakita equation. (c) Adams equation. All examples show agglomerate denomination II.

This is also the normal procedure for the use of the Kawakita function. Furthermore, the interpretation of compression parameters as measures of agglomerate deformation means that a small elastic component may possibly be included in the numerical values, since in-die compression data was used in their calculation.

σ_y *from the Heckel Equation*

The Heckel equation (8) is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the densification of the powder bed as the product. The linear form of the function is:

$$\ln \frac{1}{E} = kP + A$$

where E is the bed porosity at an applied pressure P, and k and A are constants suggested to describe particle deformability and rearrangement, respectively. The inverse of k is often proposed to be the yield strength (σ_y) of the particles.

*1/*b *and* a *from the Kawakita Equation*

The basis for the Kawakita equation for powder compression (11) is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of a pressure term and a volume term is constant. During the derivation of the equation, Kawakita introduced the degree of volume reduction C, a parameter equivalent to the engineering strain of the particle bed and thus related to bed height at applied pressures zero (h_0) and P (h_p):

$$C = \frac{h_0 - h_p}{h_0}$$

Kawakita then derived the following linear form of the function:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a}$$

where P is the applied pressure, the constant a is the total degree of volume reduction for the bed of particles and b is a constant proposed to be inversely related to the yield strength of the particles (14).

$\tau_0{}'$ *from the Adams Equation*

The Adams equation (3) was derived in order to estimate the fracture strength of single granules from in-die compression data. It models the bed of granules in the die as a series of parallel load-bearing columns. The following equation was derived:

$$\ln P = \ln\left(\frac{\tau_0{}'}{\alpha'}\right) + \alpha' \, \varepsilon + \ln(1 - e^{(-\alpha' \varepsilon)})$$

where $\tau_0{}'$ is the apparent single agglomerate fracture strength, α' is a constant related to friction and ϵ is the natural strain, related to bed height at applied pressures zero (h_0) and P (h_p):

$$\varepsilon = \ln\left(\frac{h_0}{h_p}\right)$$

At higher values of natural strain, the last term of the Adams equation becomes negligible and can be omitted, leaving a linear function. The intercept and slope of this linear part of the profile were used to calculate the compression parameter $\tau_0{}'$.

RESULTS

The deformability of all three agglomerate types studied here has been shown previously (5,6) to be dependent on the porosity of the agglomerates. In Table 1, the yield strength from the Heckel equation (σ_y) did not differ for agglomerates of different porosities but did differ according to the material composition of the agglomerates. Both the Kawakita $1/b$ values

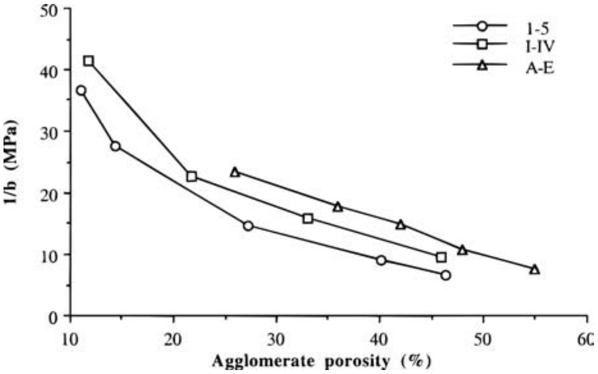

Fig. 2. Kawakita 1/*b* values during compression of agglomerate beds as a function of agglomerate porosity. Symbols are defined in the graph.

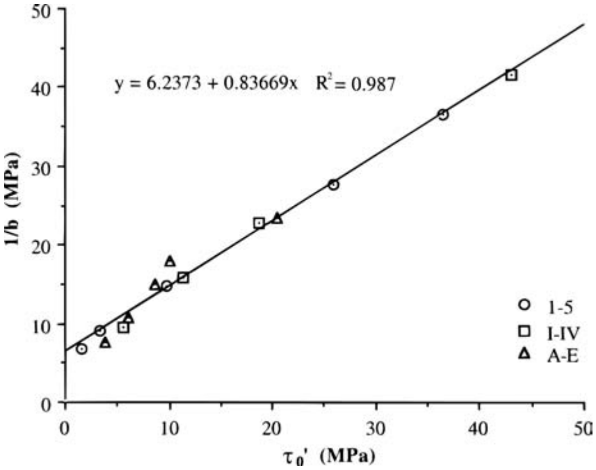

Fig. 4. Kawakita 1/*b* values versus Adams τ_0' values. Symbols are defined in the graph. The straight line represents the best fit to all data points (intercept, slope and R^2 values are in the graph).

(Fig. 2) and the Adams τ_0' values (Fig. 3) decreased with increasing agglomerate porosity for all agglomerate types, and the corresponding values for 1/*b* and τ_0' were similar in magnitude. Furthermore, a linear relationship between these values was found (Fig. 4). This is consistent with the results of Adams *et al.* (3). As can be seen in the graph, the greatest discrepancy between 1/*b* and τ_0' occurred in the lower numerical region for the values.

In physical terms, the parameter *a* in the Kawakita equation represents the total degree of volume reduction for a particle bed. As can be seen in Fig. 5, the DCP/MCC agglomerates generally had lower values for *a* than did the MCC agglomerates. Since the agglomerate types used in this study all have a similar propensity for packing when poured into a confined space, the effect seen in Fig. 5 cannot be attributed to differences in agglomerate arrangement in-die before compression. A possible explanation for the lower *a* values for the DCP/MCC agglomerates could, however, be the more rigid structure of the DCP/MCC agglomerate type, as reported previously (6).

In Fig. 6, the nominal fracture strength of single agglomerates (τ_{0s}) was plotted against the apparent agglomerate fracture strength from the Adams equation (τ_0'). As can be seen in the graph, the two categories of strength values were within the same order of magnitude. The agglomerate type 1–5 showed the most pronounced correlation between τ_{0s} and τ_0'. In contrast, there appeared to be no correlation for the agglomerate type A–E.

The permeability to air of tablets formed from agglomerates is a measure of the intergranular pore structure of the tablets (6). A low value for the permeability coefficient indicates a more closed intergranular pore structure in the tablet, which in turn is caused by a high degree of deformation of the agglomerates during compression. In Fig. 7, 1/*b* values increased with the permeability coefficient ratios. Thus, low 1/*b* values were associated with the formation of a closed pore structure.

In Fig. 8, the tensile strength of tablets was plotted against the 1/*b* parameter. The overall trend for all agglomerate types was that low values for 1/*b* were associated with the formation of mechanically strong tablets.

DISCUSSION

This study investigated the possibility of characterizing a mechanical property of agglomerated particles, relevant for

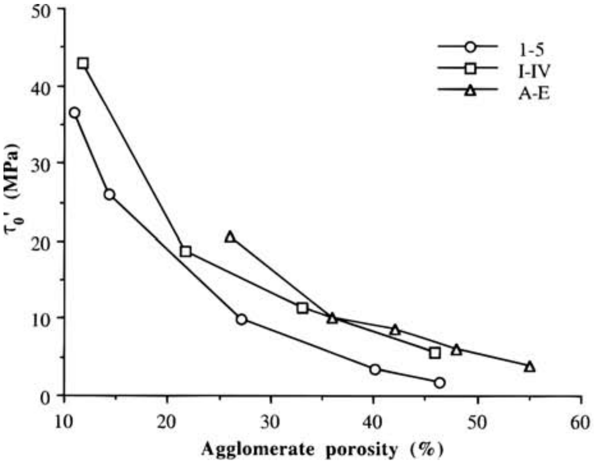

Fig. 3. Adams τ_0' values during compression of agglomerate beds as a function of agglomerate porosity. Symbols are defined in the graph.

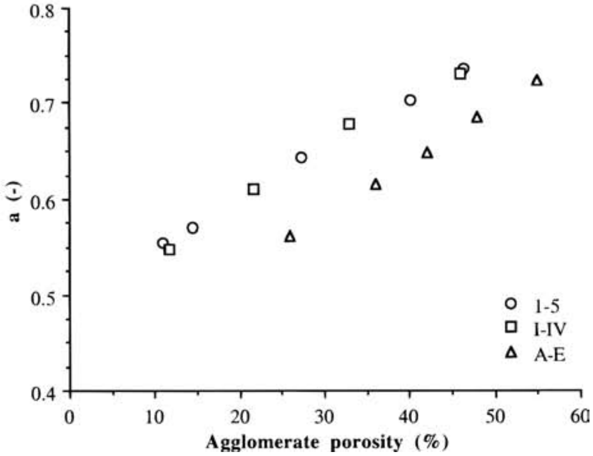

Fig. 5. Kawakita *a* values during compression of agglomerate beds as a function of agglomerate porosity. Symbols are defined in the graph.

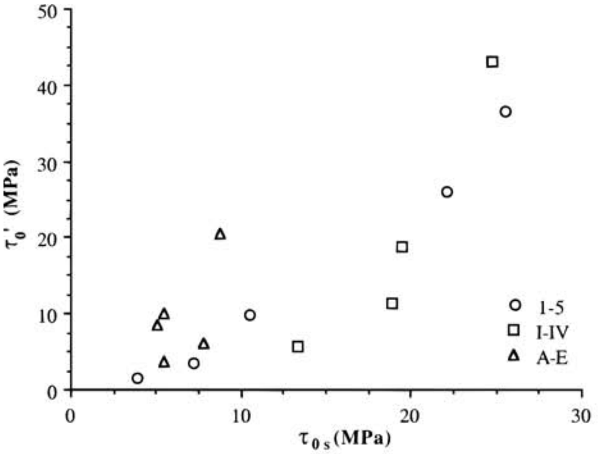

Fig. 6. Adams τ_0' values versus the nominal strength of single agglomerates (τ_{0s}). Symbols are defined in the graph.

functional tabletting behavior, from confined compression data. A common procedure in this context has been to derive the yield strength of the particles from Heckel profiles. The application of this procedure to agglomerates has, however, been questioned (7,9) and this study has shown that the use of Heckel numbers based on total porosity data is inadequate to describe the compression mechanics of agglomerates, i.e. the derived yield strength values did not vary with agglomerate porosity (Table 1). In contrast, using the Adams or Kawakita equations, parameters were derived which varied markedly with porosity and that also were related with the agglomerate composition (Figs. 2, 3 and 5).

In an earlier study (3), it was shown that the parameters 1/*b*, from the Kawakita equation, and τ_0', from the Adams equation, represent the same mechanical property of the agglomerates. A good correlation between these parameters was also obtained in this study. However, although a linear relationship was obtained, the relationship deviated slightly from a gradient of unity and a small positive y-intercept was obtained (Fig. 4). Adams and co-workers have suggested that the Kawakita parameter is less affected by the die wall friction during compression than the Adams parameter (7). Since a simplified procedure was used in this study, i.e., only one bed height was used for each powder, a friction effect could explain the deviation from a perfect relationship.

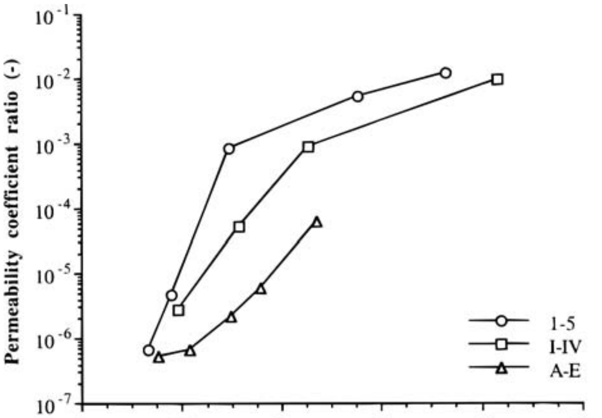

Fig. 7. Permeability coefficient ratio (ratio of the permeability coefficient of a tablet formed at 100 MPa applied pressure to the permeability coefficient of a bed of uncompacted agglomerates) as a function of Kawakita 1/*b* values. Permeability data from earlier studies (5,6). Symbols are defined in the graph.

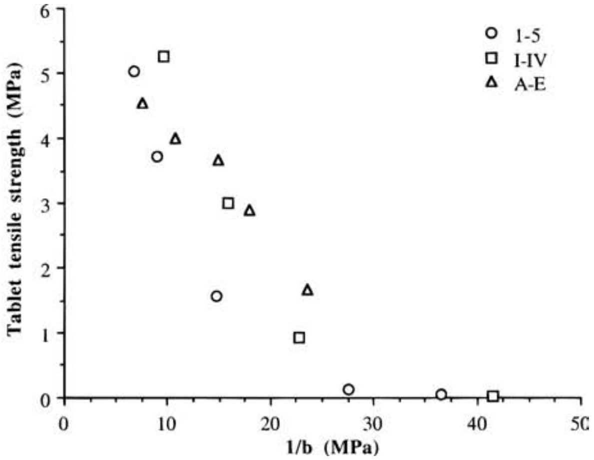

Fig. 8. Tensile strength of tablets formed at 100 MPa applied pressure as a function of Kawakita 1/*b* values. Tensile strength data from earlier studies (5,6). Symbols are defined in the graph.

Adams and co-workers (7) interpreted the physical significance of 1/*b* and τ_0' as the strength of single agglomerates during cracking or fracture by a crack-opening mechanism (tensile failure). The values for the fracture strength of the single agglomerates used in this study were indeed of the same order of magnitude as the derived 1/*b* and τ_0' parameters (Fig. 6). However, for these agglomerates, the failure process probably did not occur by a crack-opening mechanism but rather by a shearing process causing deformation of the agglomerates. This is assumed since we have earlier shown that the agglomerates used in this study remain cohered during compression and do not crack or fragment into smaller units to a significant degree (5,6).

Consequently, a general correlation between τ_0' and τ_{0s} was not obtained (Fig. 6). However, while a relatively good correlation between τ_0' and τ_{0s} was obtained (Fig. 6) for the MCC agglomerate type 1–5, prepared from different agglomeration liquid, the variation in τ_0' values were more pronounced than the variation in τ_{0s} for the other two types (I–IV and A–E). In the case of denomination A–E, the τ_{0s} values were nearly constant. The agglomerate types I–IV and A–E were prepared so that the largest intragranular pores were of similar size, irrespective of agglomerate porosity. Consequently, τ_{0s} may have been controlled by the size of the largest pores within the agglomerate while τ_0' was controlled by the pore structure in a broader sense. It is thus suggested that, for the agglomerates used in this study, 1/*b* and τ_0' represent the stress needed to initiate a flow of particles within the agglomerate, i.e., a compression shear strength. This agglomerate shear strength was related primarily with the overall porosity of the agglomerates, but also with the intragranular pore structure and composition of the agglomerates. The differences in intragranular pore structure between the two MCC agglomerate types may account for the differences in the relationship between 1/*b* and τ_0' on the one hand and agglomerate porosity on the other for the different agglomerate types (Figs. 2 and 3). It is apparent from the figures that the agglomerates containing DCP particles generally had the highest values for 1/*b* and τ_0'. This seems reasonable considering the more rigid structure of the DCP/MCC agglomerates, as discussed in an earlier study (6).

The relationship between the parameter *a* from the Kawakita equation and agglomerate porosity coincided for the two series of microcrystalline cellulose agglomerates (Fig. 5). The same observation was earlier obtained for the relationship between agglomerate porosity and the degree of compression of the agglomerates at an applied pressure of 100 MPa (6). It has been suggested that the degree of compression of agglomerates during uniaxial compression reflects the degree of deformation of the single agglomerates in terms of their flattening (15). Thus, the Kawakita *a* parameter can be described as a measure of the total degree of deformation of single agglomerates.

For the Kawakita 1/*b* parameter, different relationships to the intergranular pore structure and the tensile strength of tablets were obtained for the three agglomerate types (Figs. 7 and 8). For each type, the lower 1/*b* values were associated with the formation of tablets with a more closed pore structure and a higher tensile strength. The relationships for the three agglomerate types were, however, relatively similar and a general tendency was thus that a low compression shear strength for the agglomerates corresponded to tablets having small intergranular pores and a high tensile strength. It is, hence, concluded that the characterization of agglomerates in terms of their compression shear strength, using the Kawakita or Adams equations, can be used as an indicator of the tabletting performance of the agglomerates. In this context, it seems that the Kawakita equation may have two advantages over the Adams equation: Firstly, the Kawakita profiles showed a linear relationship over a wider range of compression pressures (Table 1) and, secondly, according to an earlier report (3), the Kawakita parameter is less sensitive to die wall friction.

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